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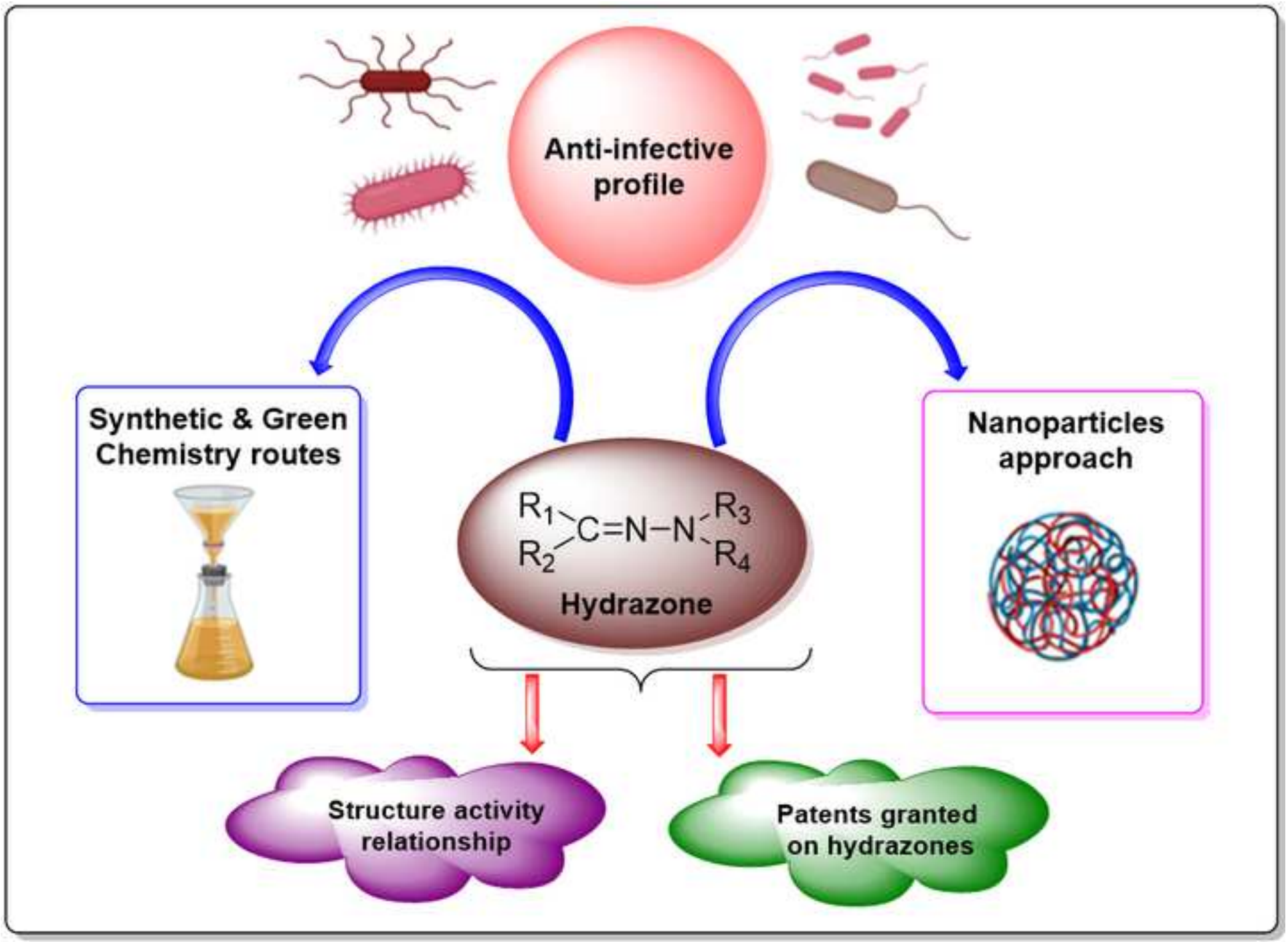
4) A brief discussion on patents filed/granted on hydrazone derivatives as anti-infective agents.

Graphical Abstract



HydrazoneComprising Compounds as Promising Anti-infective Agents: Chemistry and Structure-Property Relationship

Prabodh Chander Sharma[1*], Diksha Sharma[2], Archana Sharma[2], Neha Saini[2], Rajat Goyal[2], Monika Ola[3], Rakesh Chawla[4], Vijay Kumar Thakur[5,6*]

[1]Department of Pharmaceutical Chemistry, Delhi Pharmaceutical and Research University, New Delhi-110017

[2]Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, India,

[3]Department of Pharmaceutics, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur-425405, India

[4]Department of Pharmaceutical Chemistry, University Institute of Pharmaceutical Sciences and Research, Baba Farid University of Health Sciences, Faridkot-151203, India

[5]Biorefining and Advanced Materials Research Center, Scotland's Rural College (SRUC), Kings Buildings, Edinburgh, EH9 3JG, UK

[6]Department of Mechanical Engineering, School of Engineering, Shiv Nadar University, Uttar Pradesh, 201314, India

Abstract

Despite the adverse effects of microbial hazards on public health, major pharmaceutical firms have left the field of anti-infective development and a dramatic reduction in the number of researcher'sintricated in the quest for new specific anti-infective leads. In the non-existence of an efficient forum for antibiotics development and over usage in human beings and animals, bacteria have demoralized this potential by gradually establishing the resistance toward most of the antibiotics used. Thus, the production of novel and successful anti-infectivedrugs is urgently required to combat this resistance. Hydrazones and hydrazides have mounted as a key-skeleton for the development of active drugs, due to their important biological and pharmacological profiles.Hydrazones are being manufactured as medicines by various investigators to fight against the ailments with maximal effects and minimal toxicity.This paper focuses on the outline of the literature results of recent years, incorporating the work on the anti-infective profileof

hydrazoneanalogues. This review may also act as an excellent basisfor the development of new derivatives of hydrazone as potential anti-infective mediators.

Keywords: Hydrazones, anti-infective, antiviral, antitubercular, biological activity, structure-activity relationship.

Highlights:

1) This review highlights the potential of hydrazone derivatives as the development of newer pharmacologically active anti-infective agents.
2) SAR study of hydrazone based analogues and concise description of nanocarriers as efficient anti-infective agents.
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CONTENTS:

1. INTRODUCTION

Hydrazone ligands have attracted particular attention from researchers due to their well-known chelating capability, structural versatility and diverse range of applications. The metal complexes of hydrazones are including heterocyclic moieties containing nitrogen, oxygen and sulphur as hetero-atomshave been studiedextensively to create a probable relationship between the chemical structure and biological activity. Among them, Schiff's base hydrazones bearing nitrogen-containing moiety have attracted considerable attention due to their impressive chemical and physical properties, biological activities and also their analytical applications [1]. They are considered as the major category for the development of new drugs, determination of innovative biologically active molecules against multidrug-resistant microbial infections and can act as multidentate ligands with transition metals which demonstrate many therapeutic applications [2]. Hydrazone characterizes as a resourceful compound having a basic structure $R^1R^2C=NNR^3R^4$. Azomethine is a very important group of Schiff's bases,in which C=N is used as interesting ligand in coordination chemistry [3-5]. Hydrazone-type compounds containing an azomethine constitute an important class of compounds for the production of new drugs. The hydrazone community is well known to play a significant role in antiinfective profile [6]. Hydrazones are related to the ketones and aldehydes. Theyare formed by substituting the oxygen group of carbonyl compounds with the functional group $-NNH_2$. They act as reactants in several important reactions such ashydrazone iodination, Shapiro reaction and Bamford-Stevens reaction to form vinyl compounds. Also,theyact as an intermediate in Wolff-kishner reduction [7]. Hydrazones are mainly synthesized by refluxing the appropriate quantity of substituted hydrazines/hydrazides with ketones and aldehydes in appropriate solvents like tetrahydrofuran, glacial acetic acid, methanol, ethanol, butanol, ethanol-glacial acetic acid etc.Coupling of aryldiazonium salts with active hydrogen compounds can also synthesize hydrazones [8]. Hydrazides and hydrazones are not only intermediates but, in their own right, they are also very effective organic compounds [9]. They contain nitrogen atoms which have nucleophilic and the carbon atom has both nucleophilic and electrophilic effect. The hydrazones endowed with α- hydrogen are more potent as compared to acidic ketones. Schiff's bases produced by salicylaldehyde and its analogues with primary amines, bearing the N_2O, NO_2, N_2S or NSO donor sets, possess scrupulous biological activities [10-12]. They were commonly used in the identification and quantitative determination of various metallic compounds, analytical chemistry for the detection

and isolation of carbonyl compounds, for preparation of compounds with different structures. However, their greater physiological activity is the most important property of hydrazone derivatives [13]. Nowadays, emerging bacterial resistance is the chiefdifficulty in the handling of several infections, with the intention of that many hydrazone compounds have been prepared and examined for their anti-infective activity [14-15].

Recently, metal complexes of Schiff's bases have been fascinated the considerable interest dueto their versatile pharmacological activitiesaredescribed in **Fig. 1**. such as anti-cancer [16-17], antiviral [18-19], anti-TB [20-21], antimicrobial [22-23], anti-inflammatory [24-25], anticonvulsant [26-27], antiprotozoal [28-29], anti-HIV [30-31], anti-oxidant [32] and analgesic [33-34]. Few marketed drugs bearing hydrazone nucleus related to various biological activities are mentioned in **Fig. 6**.

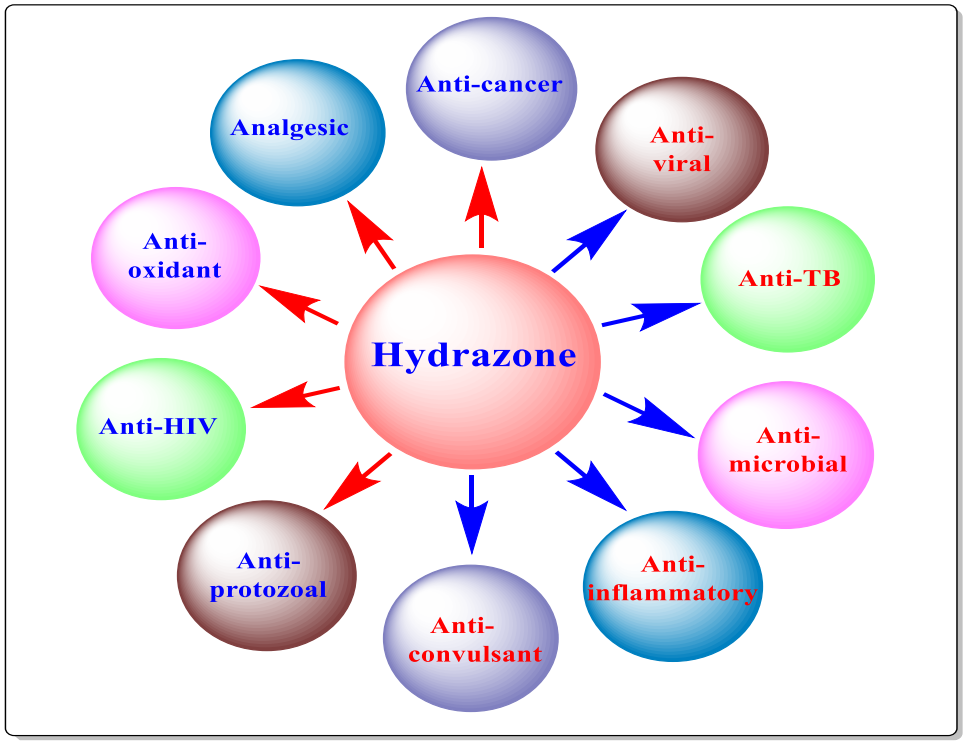


Fig.1. Various pharmacological activities of hydrazone derivatives.

Nanotechnology generally refers to an area of applied science and technology whose general theme is atomic and molecular control of matter [35]. Nanotechnology in medicine, particularly in drug delivery is already widely used and discussed in many medical fields. Not only the drug can be distributed proficiently to the site of infection with the aid of nanomaterials but even the

quantity and intensity of dosage can be regulated by avoiding therapy-related toxicity [36]. Nanoparticles are materials with at least one dimension (1-100 nm) within the range of the nanometer scale or whose basic unit is within this range in three-dimensional space(various applications, types and properties of nanoparticles are shown in **Fig. 2**).

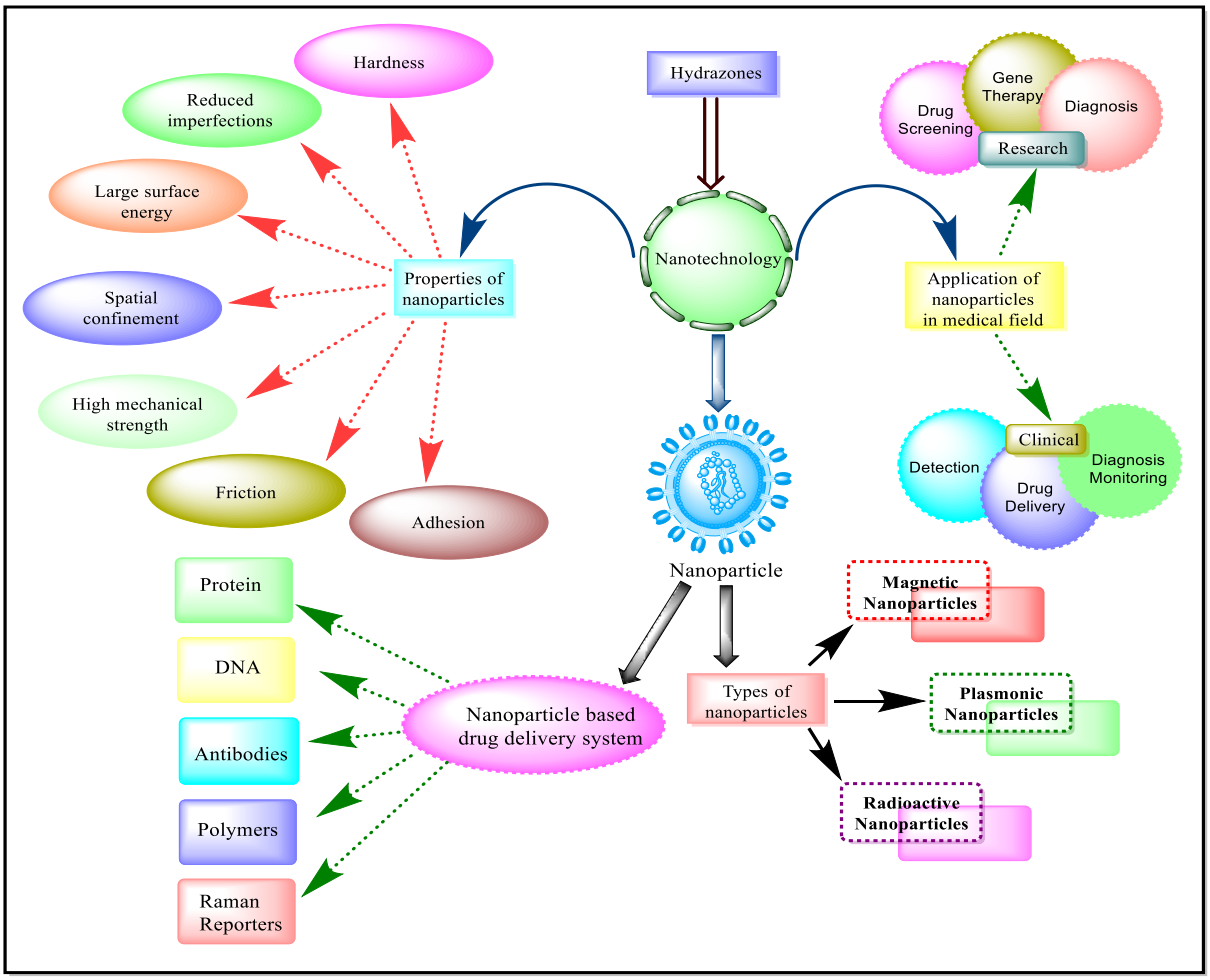


Fig. 2. Applications, types and properties of nanoparticles [37,38].

In particular, nanoparticles have a wide range of antibacterial properties towards Gram-positive and Gram-negative bacteria [39]. Because of its high surface area to volume ratio and specific physical and chemical properties, inorganic compounds in nanosize show significant antibacterial activity at low concentrations [40]. The bactericidal activity of these nanocarriers depends greatly on stability, the concentration of the growth medium and size [41]. When immersed in the biological cultural medium, nanocarriers experience various biological interfaces due to the presence of cellular molecules such as proteins, DNA, lipids, polysaccharides and flavonoids etc

[42]. Mechanism of action of nanoparticles based hydrazonesas antibacterial agents is depicted in **Fig. 3**. Viruses presents a rather significant threat to the medical, pharmaceutical and biotechnological fields as a key factor of sickness and mortality of humans. The extraordinary capacity of viruses to change easily at the new host and transitioning to a different host is really troubling and big recovery shortage. Nanotechnology provides a platform that modify or develop the drugs into nanoparticles for the treatment of various infectious diseases. As nanomedicines has smaller size they have ability to interact easily with the viruses or other microbes [43]. Mechanism of action of nanoparticles based hydrazone compounds as antiviral agents is depicted in **Fig. 4**. A millions of people are affected by tuberculosis and it is the second leading cause of death from infectious diseases after AIDS. Nanotechnology offers a a new and effective strategy to develop antimycobacterial formulations [44]. The mechanism of action of nanoparticles based hydrazone compounds as anti-tubercular agents have shown in **Fig. 5**.

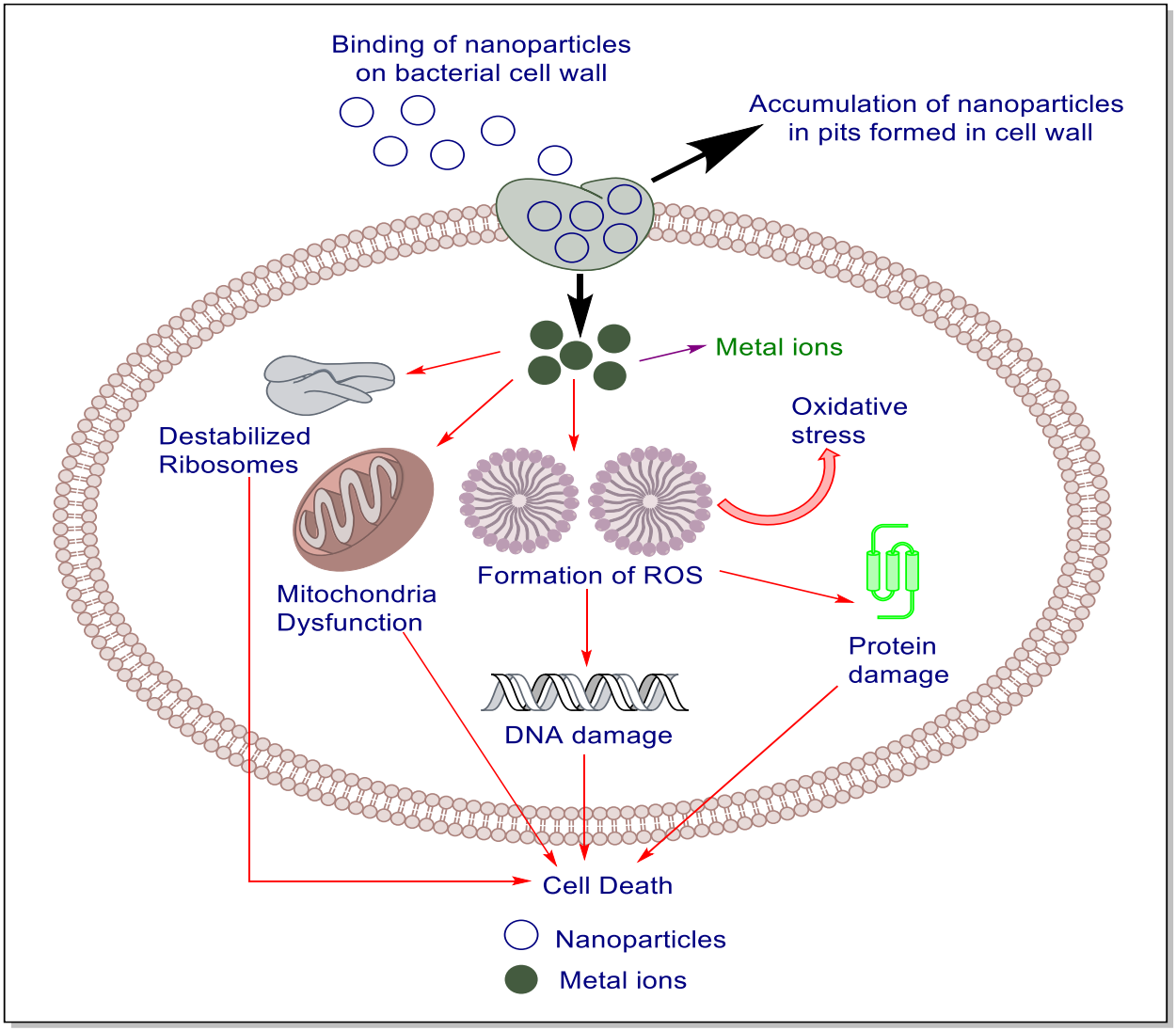


Fig. 3. Mechanism of action of nanoparticles based hydrazones compounds as antibacterialagents [45,46].

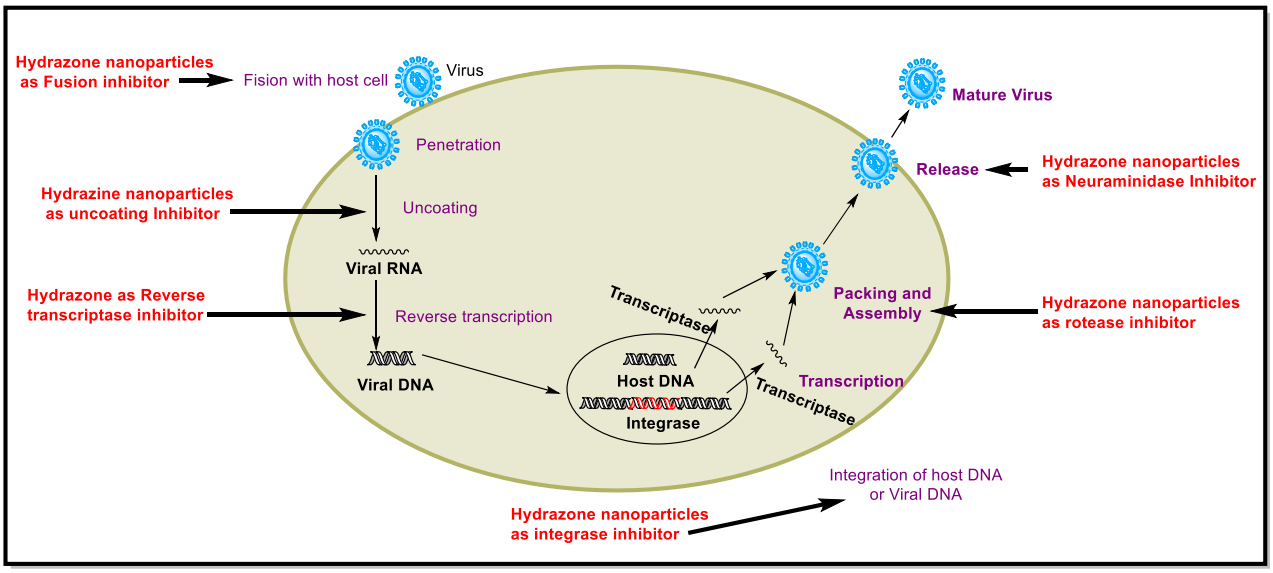


Fig. 4. Mechanism of action of nanoparticles based hydrazones compounds as antiviral agents [47,48].

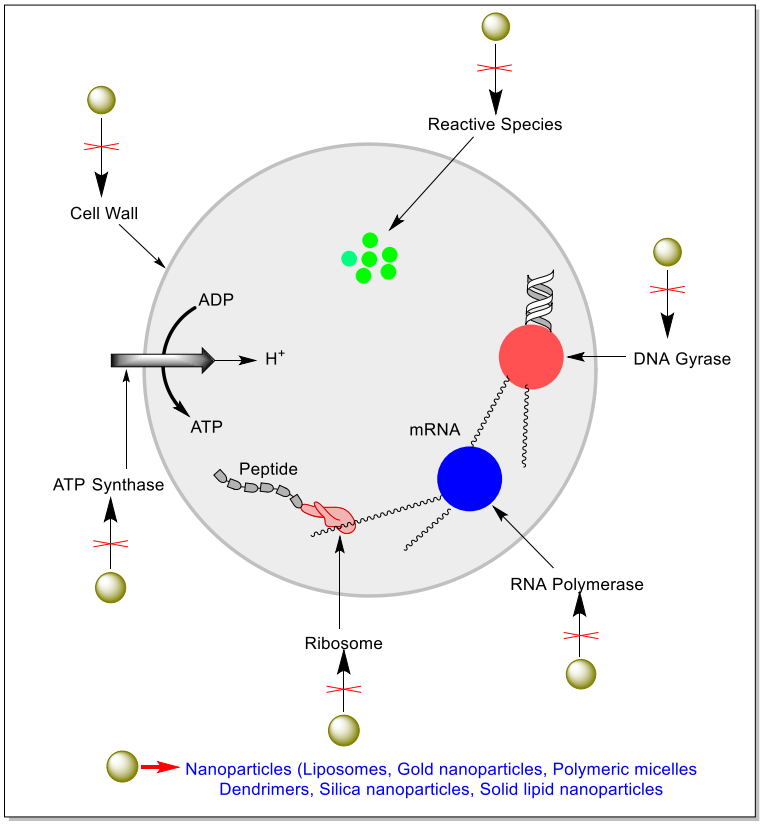


Fig. 5. Mechanism of action of nanoparticles based hydrazone compounds as anti-tubercular agents [49,50].

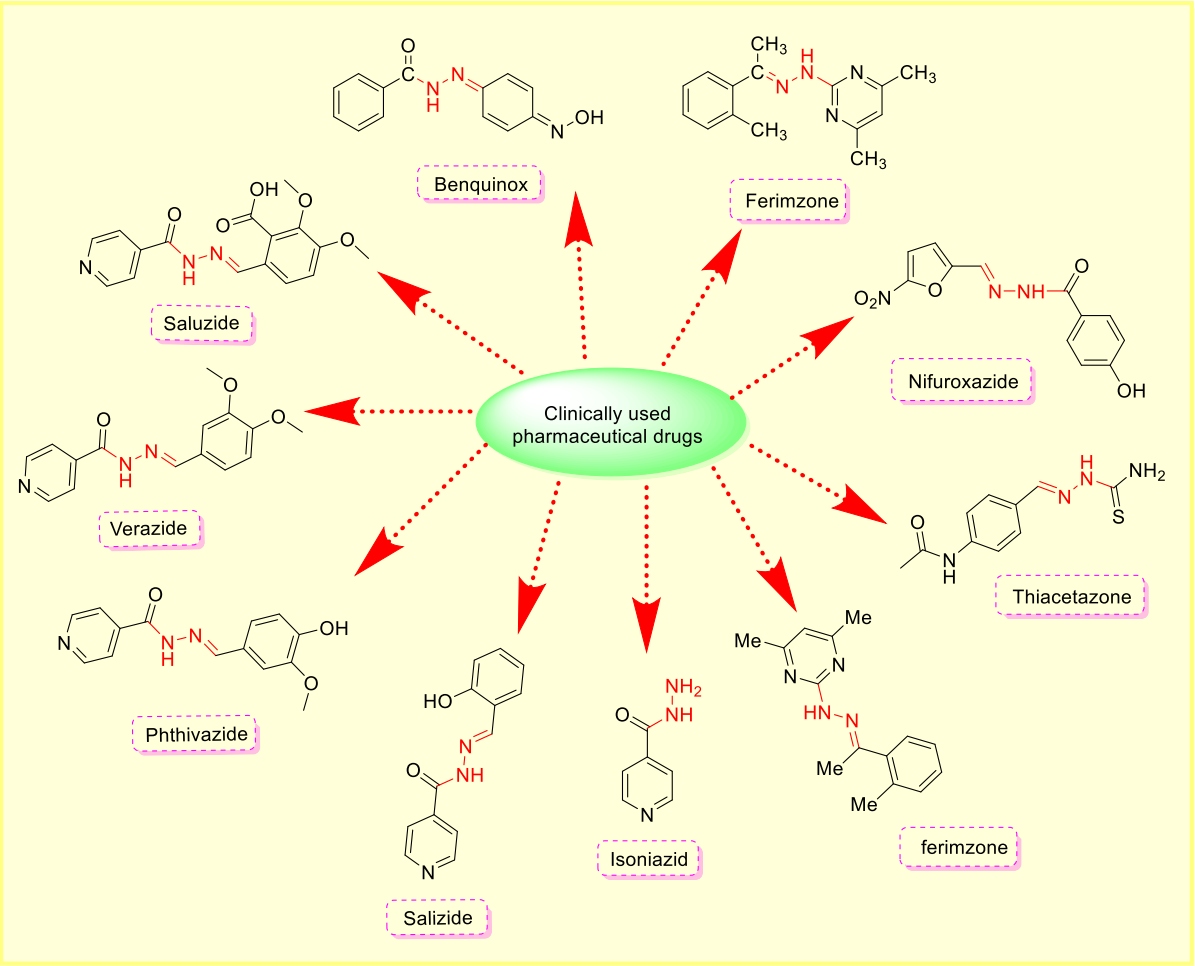


Fig. 6. Commonly prescribed marketed drugs bearing hydrazone nucleus [51-54].

2. STRUCTURE ACTIVITY RELATIONSHIP STUDYOF HYDRAZONES

The structure-activity relationship is the relationship among the 3D-structure or chemical structure of a molecule and its pharmacological activity. The SAR analysis allows determining the chemical groups accountable for triggering a biological target influence in the organism. Medicinal chemists utilize chemical synthesis methodologies to introduce new chemical groups into medicinal compounds and check its modification for their pharmacological impacts [55].

Hydrazone nucleus comprises N-NH_2 functional group, the substitution of R_1 with phenyl ring containing bromine, 3-methoxy-4-hydroxy groups showed superior antimicrobial activity in most of the analogues [56]. In some derivatives, if $R_1$is substituted with 5-nitrofuran-2-yl compounds showed better antibacterial activity [57]. Substitution of R_1 with electron-accepting groups like

F, Cl, Br and NO_2 groups displayed strong antifungal activity while analogues with heterocyclic moieties like thiophene and indole demonstrated good antimicrobial activity [58]. The most potent antitubercular activity was observed when R_1 is substituted with chlorine, bromine and nitro groups [59]. It was also found that if R_2 is substituted with benzothiazole it exhibited higher antimicrobial as well as iron-chelating activity [60]. Another substitution of R_2 with thiazole-4-(p-halophenyl) increases antibacterial activity [61]. When R_1 was substituted with hydroxyl and methoxy group compound showed superior antimicrobial activity [62]. Electron donating substituents on phenyl ring at R_2 displayed moderate resistance toward microbes [63].The SAR of hydrazones as anti-infective agents is detailed in**Fig. 7.**

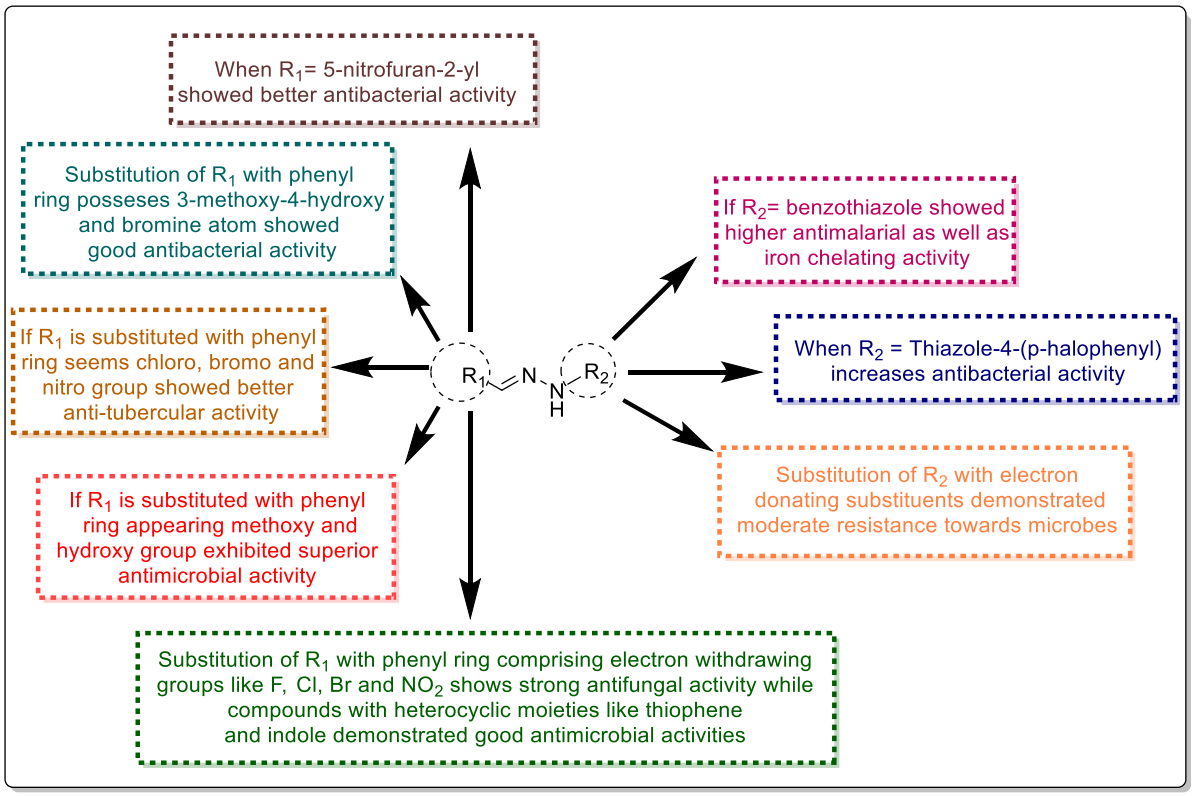


Fig. 7.SAR of the anti-infective potential of hydrazone derivatives.

3. SYNTHESIS VIA CONVENTIONAL AND GREEN CHEMISTRY

Over the decades the conventional chemical synthesis utilizes the hazardous and toxic chemicals and solvents in the manufacturing of by-products. This is an intentional implementation of chemical reactions to produce one or more products. To overcome all these unfavourable issues green chemistry came into consideration with an innovative approach for the synthetic chemist to

obtain the product with maximum yield as eco-friendly. The green chemistry approaches were observed as the best economic way to obtain a maximum number of synthetic molecules in desirable concentration. This chemical synthesis explores our potential challenges in dealing with chemical processes and products by introducing new reactions that can optimize the desired products and reduce by-products, developing new synthetic schemes and instruments that can improve chemical synthesis and searching green solvents that are eco-friendly. Microwave-assisted synthesis (MAOS) is considered as a synthetic technique through which the laboratory chemist can improve processes within a reasonable amount of time compared with traditional conductive synthetic methods .Few examples of chemical and green chemistry-based synthetic routes of hydrazone derivatives are described in **Fig. 8**.

In 2015, Velezheva *et al* have prepared a novel hybrid series of hydrazides and hydrazide-hydrazones possessing the pyrimidine and indole moiety by following **Scheme 1**[64].In 2017, Popiolek*et al* have reported a novel sequence of hydrazide-hydrazones of isonicotinic acid. The synthetic scheme used by authors is given in **Scheme 2**[57]. In 2017, Zha*et al* have reported a new series of benzo-[*d*]-thiazole-hydrazone derivatives by using the **Scheme 3** [58].In 2016, A novel series of N´-substituted-4-methyl benzene sulfonohydrazide derivatives were explored by Ghiya*et al* by using **Scheme 4** [59]. In 2016, A novel class of small molecules of benzothiazole-hydrazones were investigated by Sarkar *et al* using **Scheme 5** [60].In 2016, Gomathi*et al* have synthesized a novel class of hydrazone schiff's bases. Different hydrazone schiff's bases were prepared by using the following **Scheme 6** [65].In 2017, Fadare*et al* have investigated a new class of monocarbonyl curcumin analogues and their 2, 4-dinitrophenyl hydrazones using **Scheme 7** [66]. In 2012, Torje*et al* have reported a novel sequence of Phenothiazine-carboxaldehyde-hydrazones and bis-hydrazones through **Scheme 8, 13**[67]. In 2014, Yang *et al* presented a series of novel fluoro-substituted coumarin hydrazones via **Scheme 9**[68]. In 2015, A novel series of mesogenic substituted aroylhydrazones were explored by Singh *et al* through **Scheme 10**[69]. In 2003, Al-Zaydi *et al* described a new series of 2-arylhydrazonopropanals using **Scheme 11** [70]. In 2010, A new series of highly functionalized 4-methyl-1H-quinolin-2-ones were identified by Siddiqui *et al* via **Scheme 12**[71]. In 2011, Aboul-Fadl*et al* identified a new sequence of microwave-assisted one-step synthesis of fenamicacid hydrazides via **Scheme 14** [72].

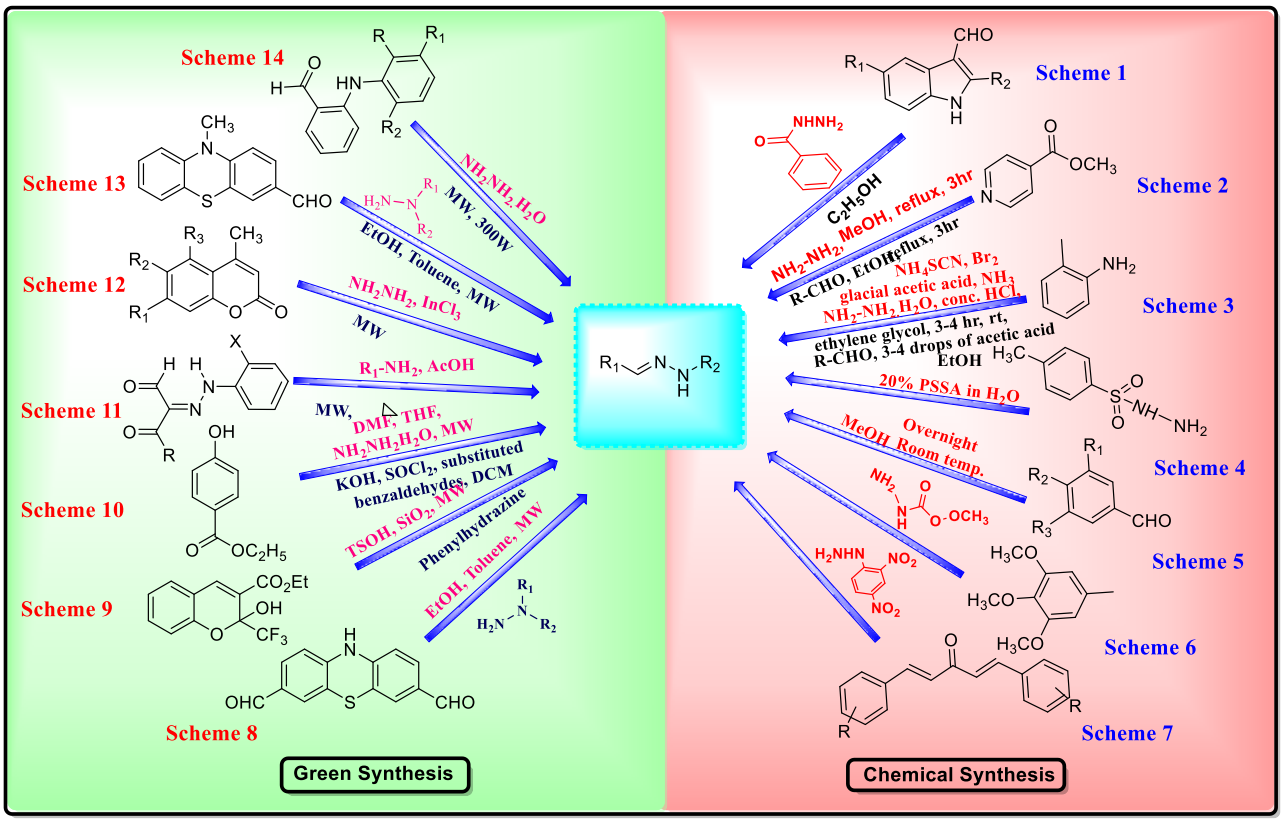
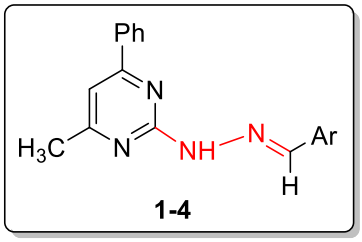


Fig. 8. The graphical representation of some green chemistry-based synthetic routes of hydrazone analogues.

4. LITERATURE SURVEY OF HYDRAZONES

4.1 Antimicrobial Activity

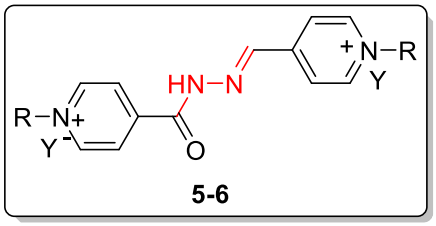
Kamal *et al* (2019), reported a novel class of 2-arylidene-1-(4-methyl-6-phenylpyrimidine-2-yl) hydrazine analogues and their antimicrobial activity was tested against two Gram-positive bacterial strains (*B. subtilis* MTCC-121 and *S. aureus* MTCC-96) and two Gram-negativebacterial strains (*E. coli* MTCC-1652 and *P. aeruginosa* MTCC-741). Most of the synthesized compounds displayed promising antimicrobial activity against both Gram-positive bacterial strains. The result showed that the compound **1** displayed the potent antimicrobial activity against*B. subtilis*and *S. aureus* with significant MICvalues of 50 µg/mland 100 µg/ml, respectively and the compounds **2**, **3** and **4**showed good activity against *S. cerevisiae* having a zone of inhibition values from 16 mmto 17 mm [73].



1-4

Comp	Ar
1	3,4-$(OCH_3)_2C_6H_3$
2	4-(Br)-C_6H_4
3	4-$(CF_3)C_6H_4$
4	4-$(NO_2)C_6H_4$

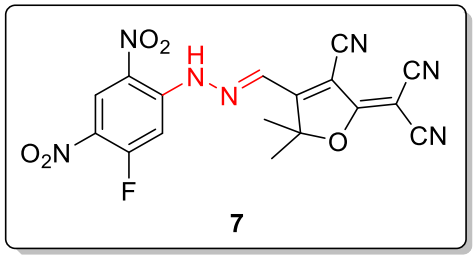
Rezki *et al* (2019), reported a novel series of pyridinium hydrazones and phenoxy conjugates. Their antibacterial activity was testedagainst two strains of Gram-positive bacteria,*Clostridium difficile* and MRSA (Methicillin-Resistant *Staphylococcus aureus*) and two strains of Gram-negative bacteria, *Escherichia coli* and *Neisseria gonorrhea* and their antifungal activity was tested against *Candida albicans*. The result showed that the compound**5** against MRSA, E.C with **(**MIC=32, 64 µg/ml) and compound **6 (**MIC=16 µg/ml) toward MRSA displayed potent antibacterial and antifungal activity [74].



5-6

Comp	R	Y
5	$(CH_2)_4OPh$	BF_4
6	$(CH_2)_4OPh$	SCN

Khattab *et al* (2019), investigated a series of novel hydrazone dyestuff's and screened towards *E. coli*,*S. aureus* and *C. albicans* for their antimicrobial activity. It was determined thatanalogue**7**displayed the effective antibacterial activity, possessing the bacterial reduction of 10±1.4%against *S. aureus* and 9±1.3% against *E. coli* and antifungal activity towards *C. albicans*, which suggested that these dyes may be used in future for thetreatment of the bacterial and fungal infection [63].



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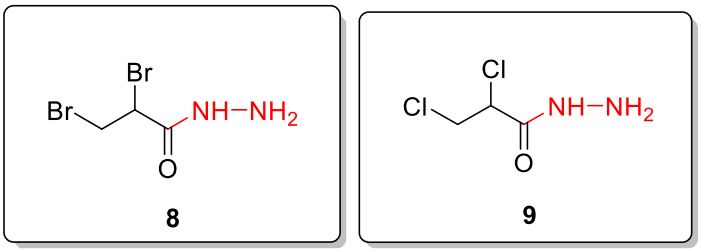
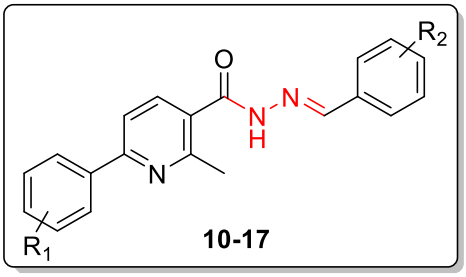
Popiolek *et al* (2018), reported a series of novel 2,3-dihalogen-substituted propionic acid hydrazides and hydrazide-hydrazones and screened for their *in-vitro* antimicrobial activity

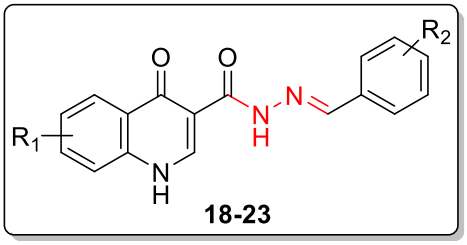
towards Gram-positive strains (*S. aureus* ATCC-25923, *S. aureus* ATCC-43300, *S. aureus* ATCC-6538, *B. subtilis* ATCC-6633, *B. cereus* ATCC-10876, *S. M. luteus* ATCC-10240, *epidermidis* ATCC-12228) and Gram-negativestrains (*B. bronchiseptica* ATCC-4617, *E. coli* ATCC-25922, *P. aeruginosa* ATCC-9027, *S. typhimurium* ATCC-14028, *K. pneumoniae* ATCC-13883, *P. mirabilis* ATCC-12453) and antifungal activity against yeast (*C. albicans* ATCC-10231*C.* and*Parapsilosis* ATCC-22019).Amongst them,the compound **8** with MICvalue of 62.5 µg/ml showedcomparable activity as compared toampicillin with MIC value of 62.5 µg/ml and the compound **9**displayed strong antibacterial activity in response to all bacterial strains,having MIC values in ranges between 31.25-125 µg/ml and MBCvalues from 62.5-250 µg/ml [57].



Abdelrahman *et al* (2017), reported two novel series ofnicotinic acid hydrazones and quinolone hydrazide analogues. They were tested for their *in-vitro* antimicrobial activity. Results showed that the compounds **10** and **11** bearing 3,4,5-trimethoxy and 2,5-dimethoxy benzylidene moieties were found to be exhibited the excellent antibacterial and antifungal activity, having significant MIC values in the range between 0.49 to 1.95 and 0.49 to 0.98 µg/ml, respectively. Also, several derivatives (**12-23)** displayed significant antimicrobial activities with MIC values in the rangebetween 1.95 to 7.81 µg/ml [62].



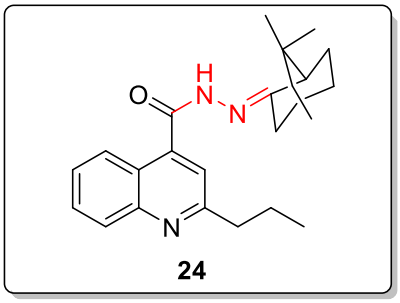
Comp	R_1	R_2	Comp	R_1	R_2
10	3-Cl	3,4,5-$(OCH_3)_3$	**14**	4-Cl	3,4,5-$(OCH_3)_3$
11	4-Cl	2,5-$(OCH_3)_2$	**15**	4-Cl	2-OH-3-OCH_3
12	3-Cl	3,4-$(OCH_3)_2$	**16**	3-Cl	4-OCH_3
13	4-Cl	2,4-$(Cl)_2$	**17**	3-Cl	2,5-$(OCH_3)_2$



18-23

Comp	R_1	R_2	Comp	R_1	R_2
18	7-Cl	4-Cl	**21**	6-Cl	2,4-$(Cl)_2$
19	7-Cl	2,4-$(Cl)_2$	**22**	6-Cl	3,4-$(OCH_3)_2$
20	7-Cl	3,4-$(OCH_3)_2$	**23**	6-Cl	3,4,5-$(OCH_3)_3$

Ajani *et al* (2017), introduced a new series of quinoline based 4-hydrazide hydrazoneanalogues and examined them for their antibacterial activity towards six bacterial species such as *E. coli*,*S. aureus*, *B. lichenformis*, *M. varians*, *P. aeruginosa* and *P. vulgaris*. Maximum of the analogues exhibitedthe highest antibacterial activity. It was concluded that compound **24** displayed the most potent antibacterial activity towards all bacterial strains having MIC valuesin the range between 1.59-0.39 µg/ml [75].



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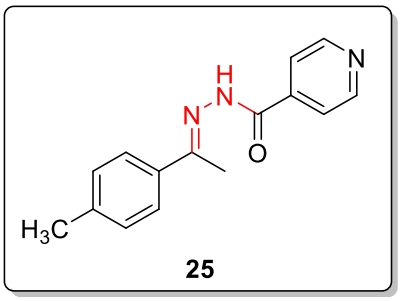
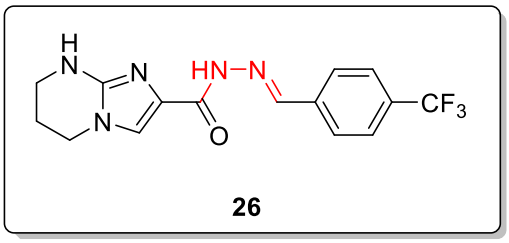
Cordeiro *et al* (2016), described some isoniazid-derived hydrazone analogues and tested for their *in-vitro* antifungal activity towards *Coccidioides posadasii*. Most of the synthesized derivativesexhibited good antifungal activity but the compound **25** showed the most potent antifungal activity towards *Coccidioides posadasii* strain with MIC value of 100-400 µg/ml. Thus, the results of the present identification revealed that in future, compound **25** may be used against fungal infections [76].



25

Kethireddy *et al* (2015), reported a novel series of 5, 6, 7, 8-tetrahydroimidazo [*1, 2-a*]

pyrimidine-2-carbohydrazide and evaluated for their antibacterial activity towards several bacterial strains. It was revealed that the analogues**26**, **27** and **28** displayed the maximum antibacterial activityagainst two bacterial strains Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*) with a zone of inhibition 30-33 mm [77].



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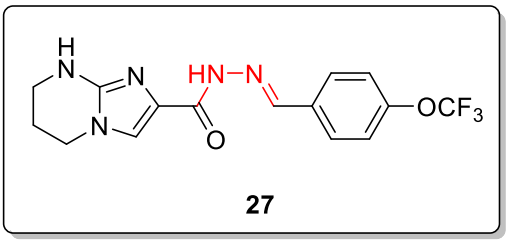

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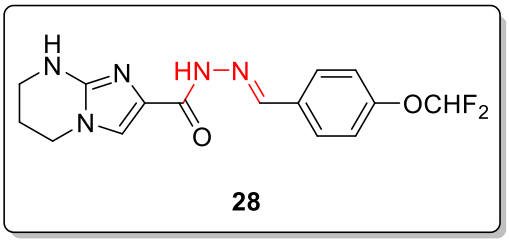
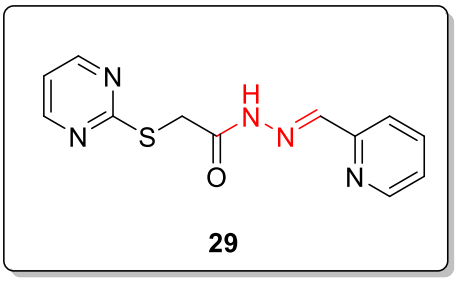


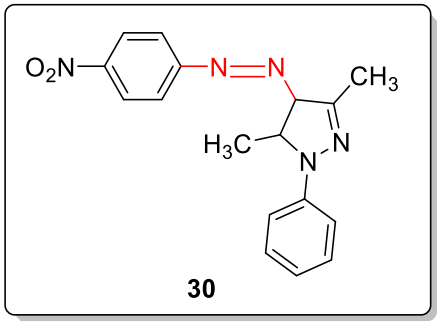
28

Kaplancıklı *et al* (2014), investigated some novel pyrimidine hydrazone derivatives and evaluated them against several species including, *E. coli, B. cereus, P.aeruginosa, B. subtilis, S.typhimurium,S. marcescens, S. epidermidis* and *C.utilis* for their antimicrobial activity. All the synthesized derivatives displayed potent antimicrobial activity. It was detected that analogue **29** exhibited a strong antimicrobial activity towards all the evaluated species with MIC values in the range between 31.25-250 µg/ml [78].



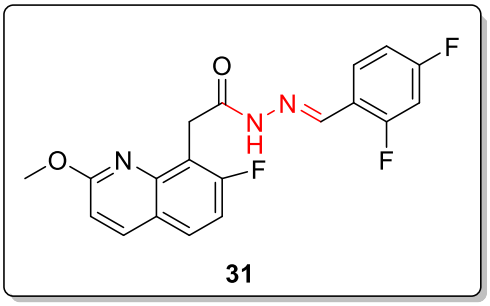
29

Singh *et al* (2013), explored a novelsequence of phenyl hydrazonescontainingpyrimidine and pyrazolederivatives and tested for their antibacterial activity. Maximum of the prepared derivatives displayed potent antibacterial activity. Among them, compound **30** showed the most promising antibacterial activity towards *B. cereus* and *B. subtilis* with MIC values of 6.25 µg/ml and 1.56µg/ml, respectively [79].



30

Sridhar *et al* (2013), scrutinized a novel series of (*E*)-N'-(substituted-benzylidene)-2-(7-fluoro-2-methoxyquinolin-8-yl) acetohydrazide-hydrazone analogues and examined them for their antibacterial activity toward several bacterial strains including, *E. coli* (MTCC-443), *S. aureus* (MTCC-96), *S. pyogenes* (MTCC-442) and *P. aeruginosa* (MTCC-424). Most of the compounds displayed anexcellent antibacterial activity. Among them, compounds **31** and **32** exhibited the strong antibacterial activity from 18-21 mm with the inhibition region. SAR study of analogues revealed that the existence of 2, 4-difluoro and 3, 4-difluoro moiety exhibited the maximum antibacterial activity [80].



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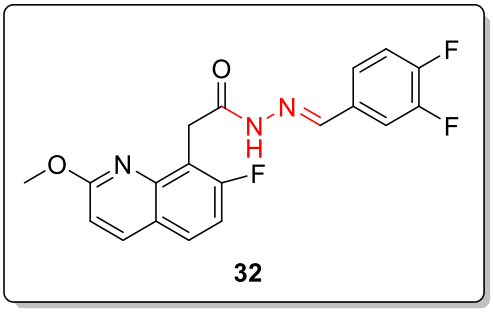
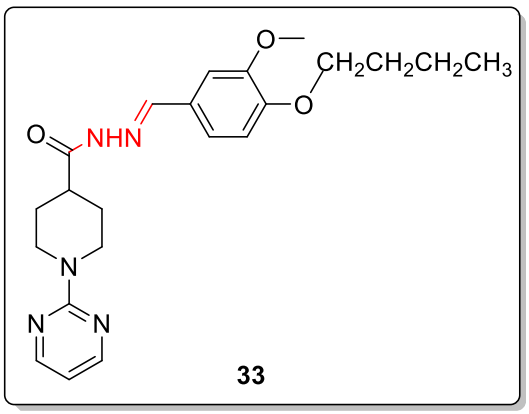
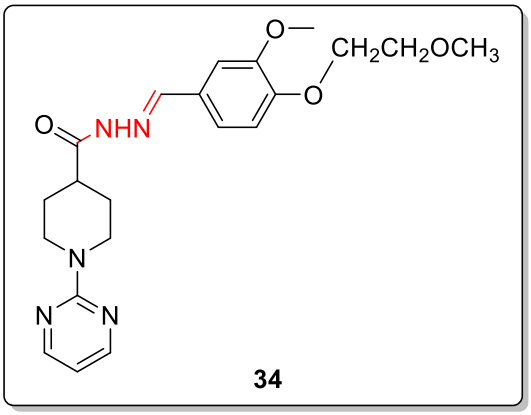


32

Govindaswami *et al* (2011), illustrated some novel vanillin related hydrazone derivatives and screened them towards two bacterial strains Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*P. aeruginosa*) for their antibacterial activity. Most of these derivatives showed moderate antibacterial activity as compared to the marketable compounds. Among them, the compound **33** was found to be most potent towards *S. aureus* (6-8 mm) and compound **34** showed potent activity towards *P. aeruginosa* (6-12 mm) at 200-250 µg/ml [81].

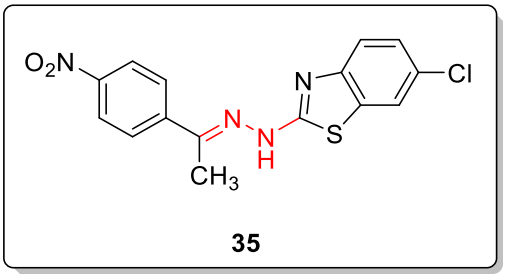


33

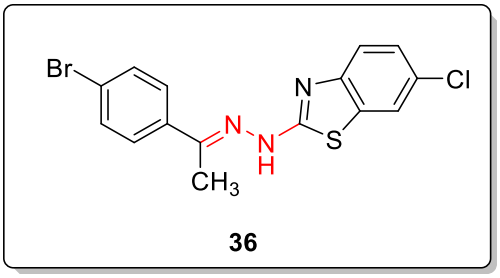


34

Asati *et al* (2011), reported a series of novel1,3-benzothiazole-2-yl-hydrazone analogues and tested for their antibacterial activity towards several bacterial strains (*E. coli, B. subtilis,P. alkaligenes, K. pneumoniae*) and antifungal activity towardsfungal strains (*A.niger, R.oryzae* and *C. albicans*). Results indicated that compounds **35** and **36** displayed the excellent antibacterial and antifungal activity towards all strains of bacteria and fungus with a zone of inhibition of 18-23 mm [82].

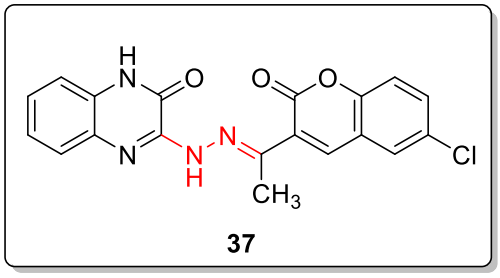


35



36

Ajani *et al* (2010), developed a new class of 2-quinoxalinone-3-hydrazone analogues by using the technique of microwave irradiation. They were evaluatedfor their antimicrobial activity whichshowed that this molecular context displayed the noticeableeffectiveness as antimicrobial agents. The result indicated that the analogue **37** exhibited utmost promising antibacterial activity and compound **38** displayed the most potent antifungal action [83].



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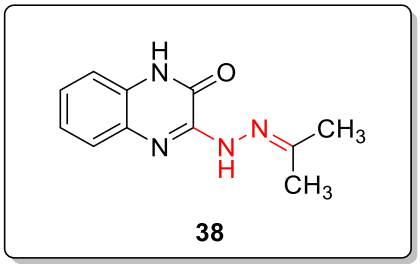
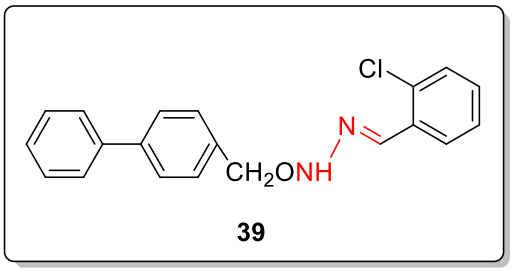
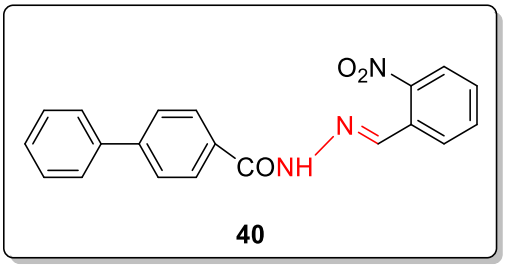


38

Deep *et al* (2010), invented a sequence of new biphenyl-4-carboxylic acid hydrazide-hydrazoneanalogues and characterized them by using analytical and spectral methods. They were evaluated for their *in-vitro* antimicrobial activitytowards two strains of Gram-positive bacteria(*B. subtilis* and *S. aureus*) and two strains of Gram-negative bacteria (*P. aeruginosa* and *E. coli*) and two fungal strains (*A. niger* and*C. albicans*). Most of the analogues displayed effective antimicrobial activity.The result showed that compound **39** exhibited the most potent antibacterial activity, having lower antifungal action and compound **40** exhibited the most potent antifungal activity, having lower antibacterial action [84].

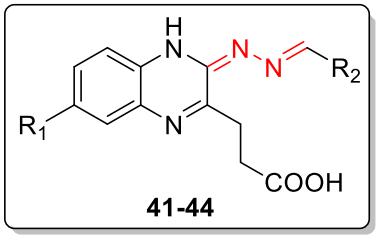


39



40

Khan *et al* (2009), described and investigated some novel hydrazone derivatives of quinoxalinone and characterized them by FT-IR and ^{1}H-NMR data. Their *in-vitro* antimicrobial activity was evaluated towardstwo bacterial strains Gram-positive bacteria (*S. aureus* ATCC-29213) and Gram-negative bacteria(*E. coli* ATCC-25922).It was revealed that compounds **41, 42, 43** and **44** exhibited the comparatively good activity towards both types of bacterial strains, using ofloxacin as the reference drug. Also, this study showed that the compounds containing extremely electronegative substituents (chloro and fluoro) at the *para*-position of phenyl ring displayed better activity in comparison to the analogues containing these atoms either at ortho or meta-positions or the other analogues comprisingfewer electronegative/electropositive substituents at these positions [85].



41-44

Comp	R_1	R_2
41	H	4-F-C_6H_4
42	H	4-Cl-C_6H_4
43	CH_3	4-F-C_6H_4
44	CH_3	4-Cl-C_6H_4

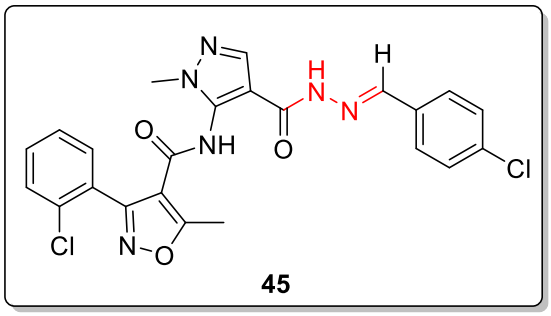
4.2 Antiviral Activity

In the early 20th century, infectious diseases were the most common cause of human illness leading to the death [86]. Malignant tumors and viral infections represent the world's most significant threats to public health [87]. Based on current scenario, the spread of Corona Virus Disease (COVID-19) has become a major global public health event, threatens to people's physical and mental health and even life protection, affecting all age groups with a higher incidence in geriatric populations and chronic diseases [88,89]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of corona virus that causes coronavirus disease (COVID-19). In these days, spread of SARS-CoV-2 virus through air has become a controversial subject among scientists. Various organizations provide standard methods for monitoring the biological agents [90].

Recently available most of the therapeutically active antiviral medications are intended against human immune deficiency virus (HIV), herpes viruses (best known for causing the cold sores and genital herpes, but causing a wide variety of diseases), hepatitis B and C viruses and influenza A and B viruses [91]. However, prolonged treatment with antiretroviral therapy results in the disease progression. Nowadays, a great advancement requires in the production of newer drugs which may serves as targeted essential aspects of the HIV life cycle in the field of research and development. This includes viral entry (fusion inhibitors) and penetration into the host genome (integrase inhibitors).There is an increasing demand of New Chemical Entities (NCE's) and drug substances due to the increased resistance, recurrence and spread of various diseases, growing number of immunocompromised patients and emergence of many new infections. These have made it possible to identify new medications that are useful in clinical therapy in order to face good health conflict [92]. A large number of hydrazone derivatives have been synthesized and studied for the wide range of antiviral activity.

Yang *et al* (2018),developed a novel series of pyrazole-hydrazone analogues bearing an isoxazole skeleton. They were evaluated for their antiviral activity by using antiviral bioassay(half-leaf method)which indicated that few derivatives showed better *in vivo* antiviral activity towards tobacco mosaic virus (TMV). Amongst, compounds **45, 46** and **47** displayed the best protection activity, inactivation activity and therapeutic activity against TMV, respectively, which were greater thanstandard drug Ningnanmycin. This study confirmed that this series of

novel pyrazole-hydrazone analogues containing an isoxazole amide moiety can be considered for the further development as a new class of tobacco protection agents [93].



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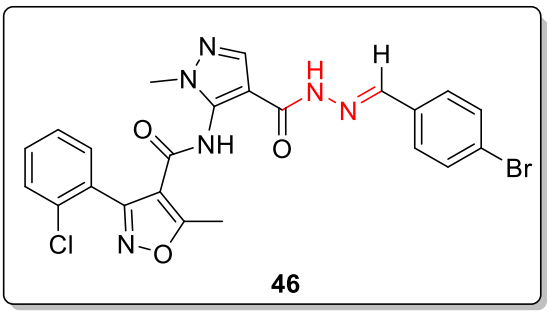
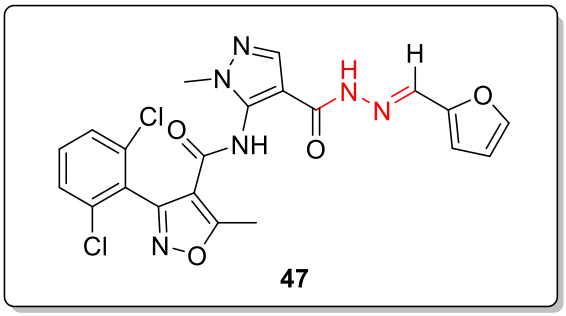
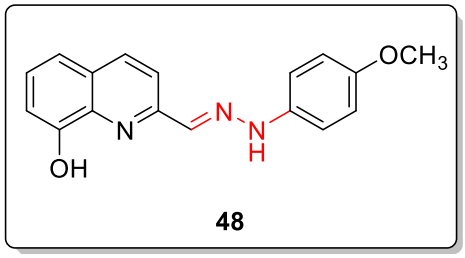


46



47

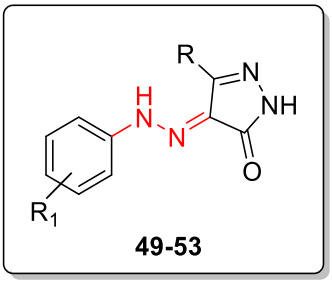
Shah *et al* (2018), reported a new class of 8-hydroxyquinoline-hydrazone derivatives and characterized them by using ^{1}H-NMR, ^{13}C-NMR, HRMS and IR techniques. All the synthesized analogues were tested for their anti-HIV-1 activity. Results showed that the compound **48** was found to be most potent (IC_{50}: 1.88 and 6.27 µM, TI: 73.82 and 22.07, toward HIV-1_{VB59} and HIV-$1_{UG070,}$ respectively). This compound **48** (4-methoxy substitution on phenyl ring) exhibitedthe highest anti-HIV-1 activity (6.5 and 1.6 folds higher) with selectivity (TI approximately 12 and 3 times) against both HIV-1 strains as compared to the parent compound. Thus, the compound **48** can be considered as a lead for improving its anti-HIV-1 potential [30].



48

Singh *et al* (2013),prepared a novelsequence of phenyl hydrazonecomprisingpyrazole and pyrimidine derivatives and evaluated against TZM-*bl* cells for their anti-HIV activity at the concentration of 50 µg ml^{-1}. The result indicated that most of the analogues displayed

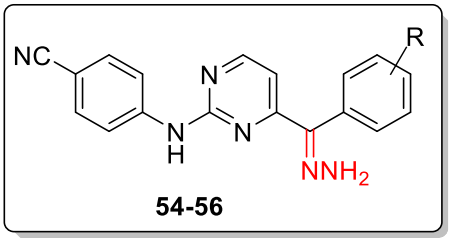
promisinganti-HIV activity. It was observed that at a test dose, compounds**49, 50, 51** and **52** displayed more than 85% inhibition of HIV while analogue **53** showed 98% inhibition. It was demonstrated that these designed molecules have the possibility of introducing the chemical diversity around the core skeleton to generate newer potent molecules[79].



49-53

Comp	R	R_1
49	CH_3	4-NO_2
50	CH_3	4-Br
51	NH_2	4-NO_2
52	NH_2	3-Cl
53	NH_2	4-Br

Ma *et al* (2011), invented a novel sequence of aryl-2-[(4-cyanophenyl)amino]-4-pyrimidinone hydrazone derivatives and tested toward human immunodeficiency virus (HIV)-1 in MT-4 cells for their antiviral activity. Most of the compounds showed tremendous activity towards wild-type HIV-1, with EC_{50} values between 1.7-13.2 nm. Among them, the compounds **54** (EC_{50}=2.4±0.2nm, SI=18461), **55** (EC_{50}=2.6±1.2 nm, SI=2673) and **56** (EC_{50}=1.7±0.6 nm, SI=5762) presented the effective activity as compared to ETV towardstrains of wild-type HIV-1. Furthermore, the activity of compounds **54** and **56** against HIV-1 $RT_{(WT)}$, CCR5-tropic HIV, and CXCR4-tropic HIV indicates that the target of hyd-CH_2-DAPYs is wild-type RT only [94].

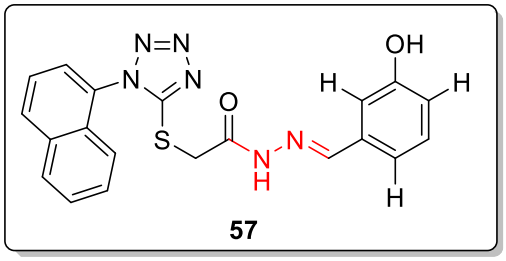


54-56

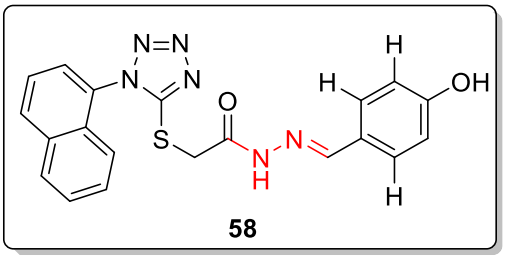
Comp	R
54	4-CH_3
55	2-Cl
56	2-Br

Zhan *et al* (2010), reported a novel sequence of N´-arylidene-2-[1-(naphthalen-1-yl)-1H-tetrazol-5-ylthio] acetohydrazide analogues as nonnucleoside reverse transcriptase inhibitors (NNRTIs)and screened them using IIIB strain and ROD strain for their *in vitro* HIV-1 and HIV-2 activity, respectively. The activity was scrutinized via the retardation of virus persuaded cytopathic effects in human T-lymphocyte (MT-4) cells. Results revealed that the analogues **57** and **58** showed EC_{50} values of 29.62 µM (CC_{50} of 169.24 ± 23.83 µM)and 31.62 µM (CC_{50}> 309.06 µM) and resulting in selectivity index of 6 and >9, respectively. The compounds

nevirapine (NVP), efavirenz (EFV), delavirdine (DLV) and zidovudine (azidothymidine, AZT) were used as the reference drugs [95].

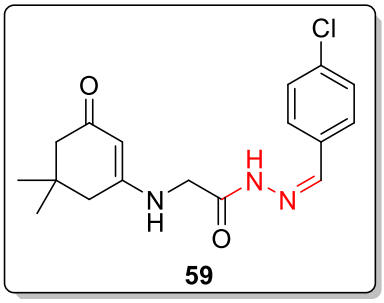


57



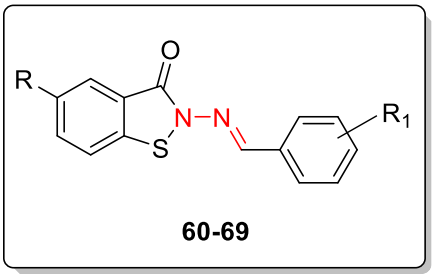
58

El-Sabbagh *et al* (2009), synthesized a novel series of hydrazone derivatives from cyclic β-diketone and their structures were characterized by utilising elemental analysis and numerous spectroscopic techniques. They were screened toward Hepatitis-A Virus (HAV) for their antiviral activity by using the plague infectivity reduction assay method. It was detected that the compound **59** demonstrated the tremendous antiviral activity, in comparison to the reference drug amantadine [87].



59

Vicini *et al* (2009), explored a novel sequence benzo[*d*]isothiazolehydrazoneanalogues and examined for their anti-HIV activity in MT-4 cells culture toward wild type strains of HIVand HIV-1 which carry clinically appropriate genetic variations (EFV^R, Y181C and K103/ Y181C). It was revealed that in this evaluated series, benzo[*d*]isothiazol-3(*2H*)-one moiety was vital for anti-HIV activity. Results showed that analogues **60** and **61** displayed decent activity towards HIV-1 wild type strains, while the analogues **60, (62-69)** exhibited good activity towards EFV^R mutant. It was observed that only one analogue **64** presented noteworthy activity towards Y181C mutant [96].

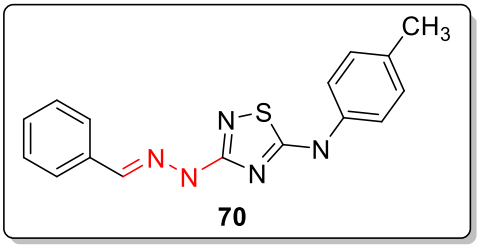


60-69

Comp	R	R_1	Comp	R	R_1
60	H	H	**65**	H	4-OH
61	H	4-F	**66**	CH_3	4-F
62	H	3-F	**67**	CH_3	4-Cl
63	H	4-Cl	**68**	CH_3	3-NO_2
64	H	3-NO_2	**69**	CH_3	3-OH

4.3 Anti-TB Activity

Dogan *et al* (2020), developed a novel series of thiadiazolylhydrazonesand were tested for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv using Microplate Alamar Blue Assay (MABA) method. Most of the compounds showed good antitubercular activity in the range of MIC 0.78-6.25 µg/ml. Compounds**70**and**71**showed prominent antitubercular activity at MIC of 0.78 µg/ml. It is concluded that these compounds possessed antitubercular activity due to enoyl acyl carrier protein reductase (InhA) as the possible target enzyme [97].



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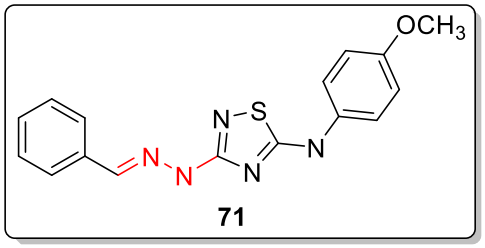
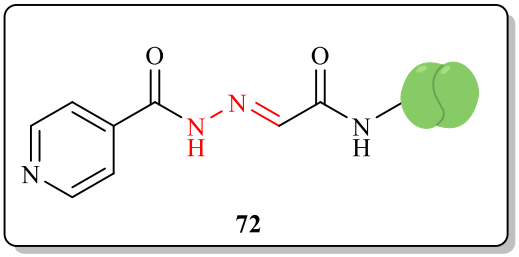


71

Sutar *et al* (2019), prepared a new series of isoniazid-transferrin conjugates viz TF-IH and TF-IG (**72, 73).** They were further investigated for their *in-vitro* anti-tubercular activity. These conjugates were found to have higher pH-dependent stability and better anti-TB activity than free isoniazid. Transferrin-IH conjugates exhibited a significant drop in the colony-forming unit at 0.39 µg/ml conc. than Transferrin-IG & free INH during *ex-vivo* studies. Hence, it's evident that the conjugation of anti-tuberculosis agents with transferrin improves the potency and efficiency of drugs [98].



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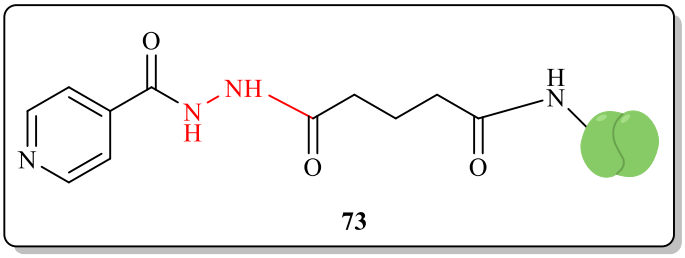
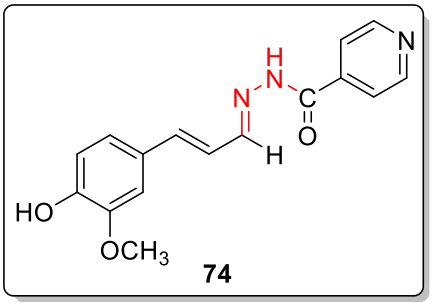


73

Sampiron *et al* (2019), presented a novel sequence of hydrazone, benzohydrazones and isoniazid-acylhydrazones derivatives and determined for their *in vitro* antitubercular activity against *M. tuberculosis* $H_{37}Rv$ and other various strains. All compounds revealeddecent activity at MIC of 0.12-250 µg/ml. They exhibited significant MIC at both pH 6.8 and 6.0. Compounds **74-77** with isoniazid-acylhydrazones showed prominent results. Based on the above results, isoniazid-acylhydrazones can be used for new drug development as antitubercular agents [99].



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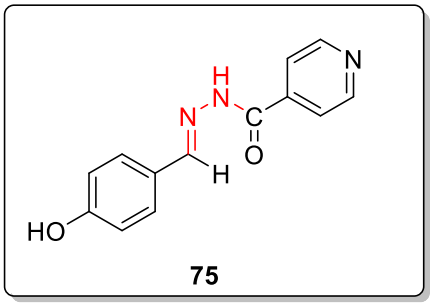

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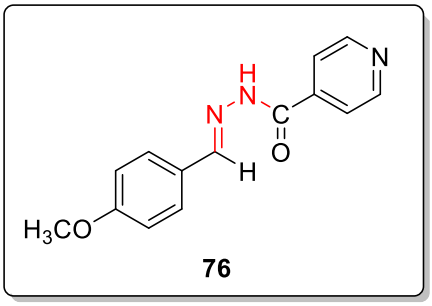

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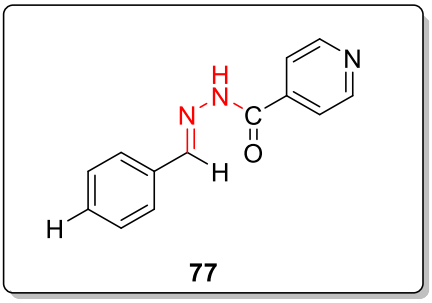
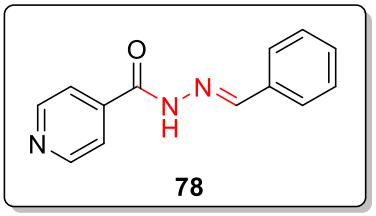


77

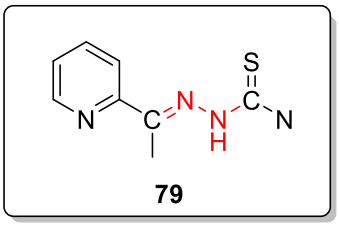
Hakkimane *et al* (2018), reported a novel sequence of rifampicin-loaded poly lactic-co-glycolic acid nanoparticles and isoniazid derived isoniazid benz-hydrazones and testedfor theiranti-tubercular activityagainst the H37Rv strain of *Mycobacterium tuberculosis*. It was observed that

analogue **78** showed potent antimycobacterial activity, better stability and sustain release properties for one month. All the synthesized compounds were found to be better anti-TB agents and have more efficacy in drug delivery than free forms [100].



78

Bonnett *et al* (2018), explored a series of hydrazones and examined for their antimycobacterial activity toward non-replicating *M. tuberculosis* species. All the parameters like Minimum Inhibitory Concentration (MIC), Low Oxygen Recovery Assay (LORA) and Minimum Bactericidal Concentration (MBC) were recorded for tested compounds. Most of them showed excellent anti-tubercular activity. Amongst, two compounds **79** and **80** exhibited the remarkable activity under hypoxic conditions than aerobic culture. In a nutshell, hydrazones have prominent activity as antitubercular agents [101].



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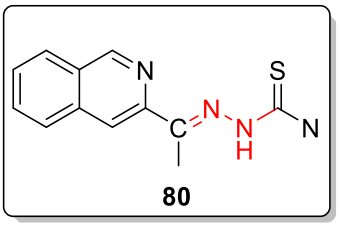
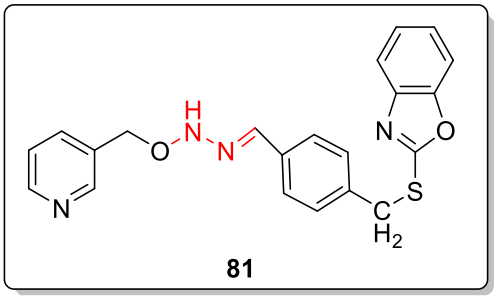


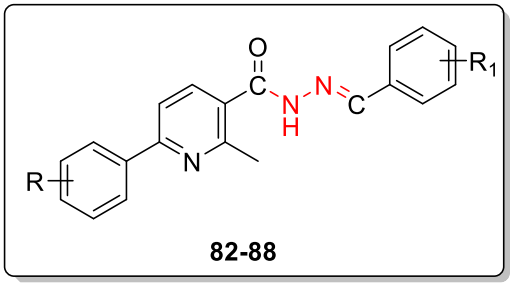
80

Lu*et al* (2017), reported two novel series of benzylsulfanyl benzo-heterocyclic amides and hydrazones derivatives. These compounds were assessed for their anti-TB activities and some of the isonicotinylhydrazones derivatives possessed decent anti-tubercular activity towards the H37Rv strain of *M. tuberculosis.* MIC values of these compounds were found to be better than isoniazid, moxifloxacin, streptomycin and PA-824. Further, *in-vivo* studies explored that compound **81**can be used as a new anti-TB agent as it significantly lowers the activity of mycobacterium in H37Ra infected mouse model [102].



81

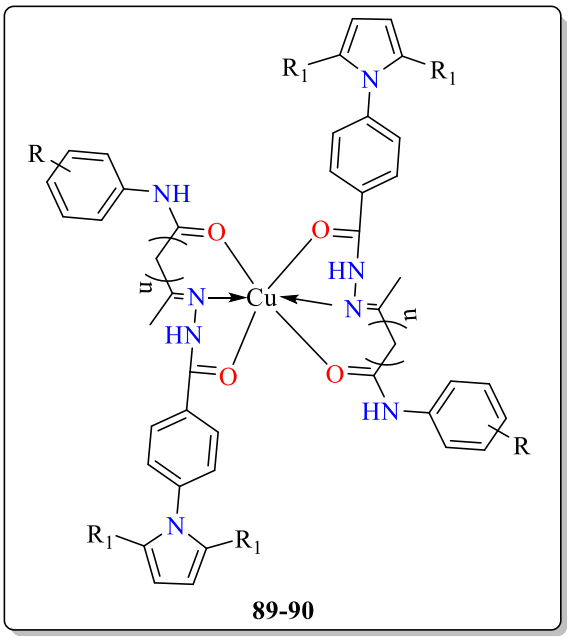
Abdelrahman*et al* (2017), have identified a new sequence of pyridine and quinoline based hydrazoneanalogues. The prepared analogues were evaluated for their anti-TB activity. Results concluded that analogues **82, 83** and **84** displayedremarkableantimycobacterial (MIC = 0.39 µg/ml). Whereas, the compounds **85, 86, 87** and **88** displayed excellent antimycobacterial activity(MIC= 0.78 µg/ml) [62].



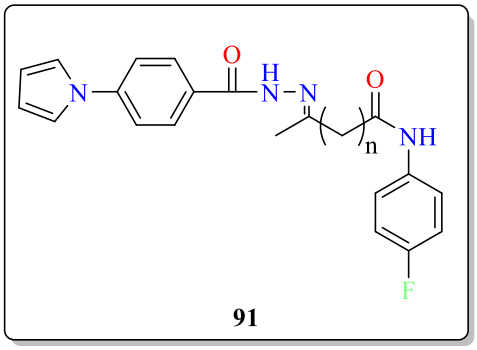
82-88

Comp	R	R_1
82	4-Cl	2-OH-3-OCH_3
83	4-Cl	2,5-$(OCH_3)_2$
84	3-Cl	2,5-$(OCH_3)_2$
85	3-Cl	3,4-$(OCH_3)_2$
86	3-Cl	3,4,5-$(OCH_3)_3$
87	4-Cl	3,4,5-$(OCH_3)_3$
88	4-Cl	4-OCH_3

Joshi *et al* (2016), prepared anovel sequence of pyrrolyl hydrazones and their Cu(II) complexes. The compounds were analyzed *in-vitro* for their anti-tubercular activity against the bacterial strains of *M. tuberculosis*. As compare to ligands metal-complexes were found to be more potent. Compounds **(89-91)** showed appreciable anti-TB activity with MIC value of0.8 µg/ml against standard drug rifampicin. These compounds were able to bind more than 60% with enzymes at a concentration lower than 5µM [103].



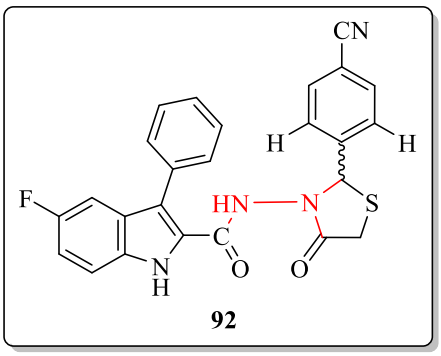
89-90



91

Compounds	R_1	R_2
89	H	4-Br
90	H	4-F

Cihan-Ustundağ *et al* (2015), developed a novel series of indoyl hydrazones and indole-based 4-thiazolidinones. The synthesized analogues were examined *in-vitro* for their anti-tubercular activity towards *Mycobacterium tuberculosis* H37Rv. It was found that compounds **92-96** showed excellent anti-TB activity with a 10-fold lower concentration of mammalian cell toxicity with MIC value of 6.25 to 25.0 µg/ml [104].



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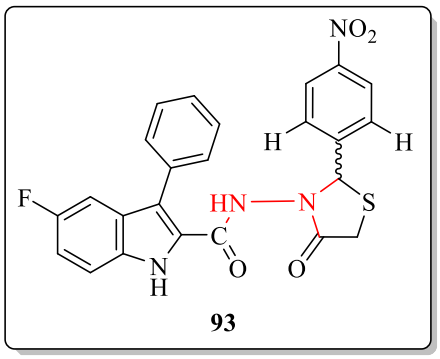

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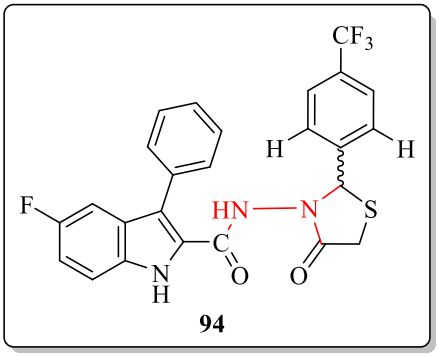

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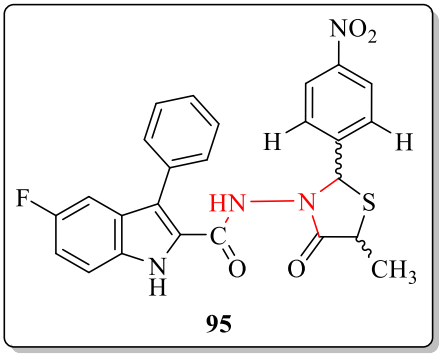

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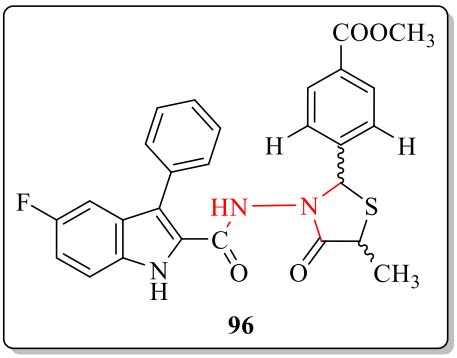
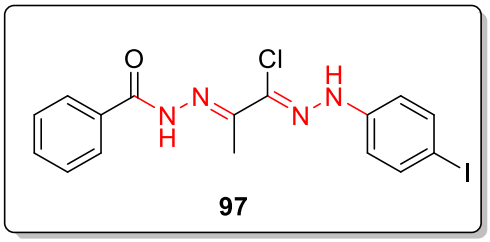


96

Abdel-Azi*et al* **(2015),** presented three novel series of halophenyl bis-hydrazones and tested for their antimycobacterial activities. Results indicated that analogues **97-101** possessing broad antimicrobial activity against *Mycobacterium tuberculosis*. The above mentioned five analogues can serve fairly well to recognize chemotherapeutics of broad-spectrum anti-TB [105].



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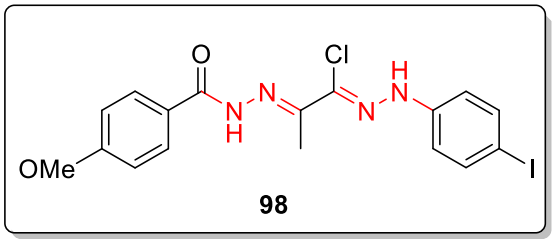

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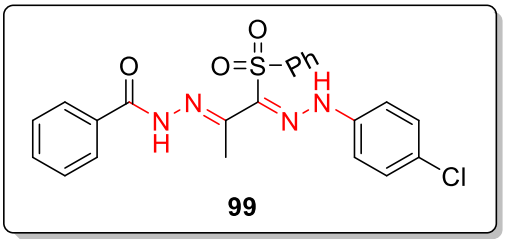

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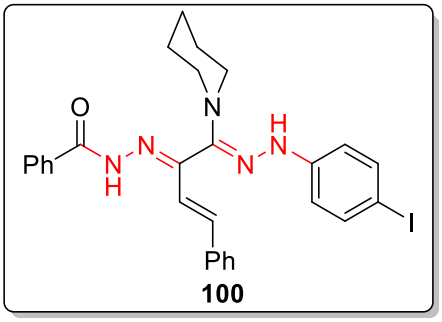

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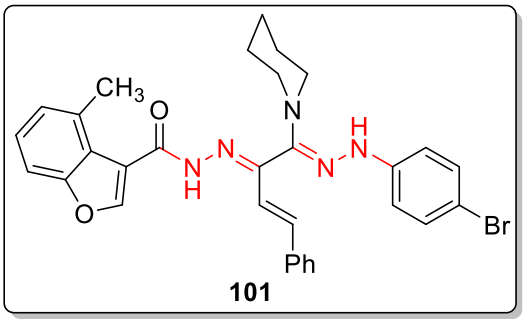
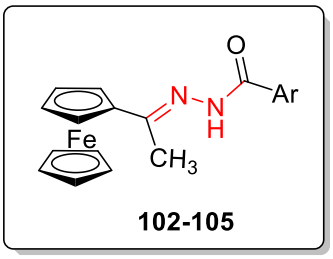


101

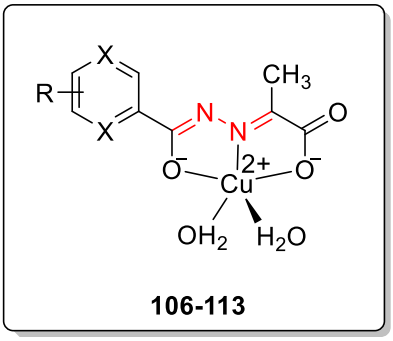
Dandawate *et al* (2014), investigated a new sequence of four analogues (**102-105**) of ferrocenylhydrazones under varied iron conditions and their β-cyclodextrin (CD) inclusion complexes were synthesized and examined for their anti-tubercular activity. It was discovered thatlow MIC values (0.5-128 µg/ml) against 7H9 medium were shown by cyclodextrin inclusion complex of INH. FBHZ and its cyclodextrin inclusion complex was found to be the most significant amongstthem and exhibited MIC values of 1.0 and 0.5 µg/ml. Cyclodextrin conjugates hold good potential for the production of antitubercular drugs under varied iron condition [106].



102-105

Comp	Ar	Comp	Ar
102		104	
103		105	

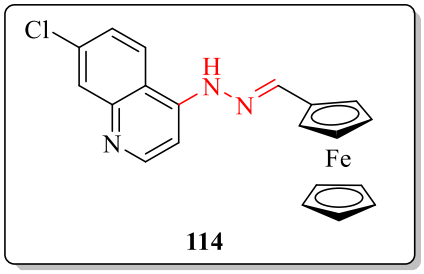
Jamadar*et al* (2012),arranged a new sequence of pyruvate based hydrazones and tested toward *M. tuberculosis* using middle brook 7H9 medium. About eight of the pyruvate hydrazones and its sodium salts displayed inactivity in their anionic form. On the other side, prominent antimycobacterial activity was displayed by their neutral Cu (II) complexes (**106-113**) under elevated iron (8 µg Fe per ml) condition. The complexes $[Cu(L^1)(H_2O)_2]$ – $[Cu(L^8)(H_2O)_2]$ showed MIC values of <0.5 - 2 µg/ml [107].



106-113

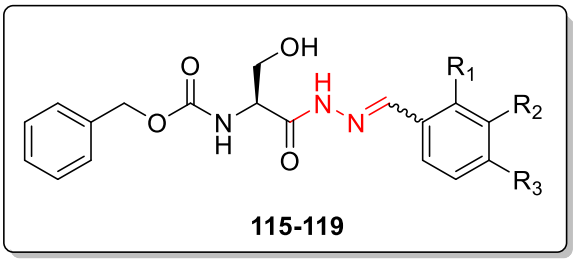
Comp	X	R	Comp	X	R
106	CH	4-CH_3	**110**	CH	4-CH_3
107	CH	4-NO_2	**111**	CH	3-F
108	CH	4-$(CH_3)_3$	**112**	CH	3-OH
109	CH	4-NO_2,3-CH_3	**113**	N	H

Mahajan *et al* (2011), introduced a novel series of ferrocene based hydrazonesand evaluated for their anti-tuberculosis activity towards *Mycobacterium tuberculosis*. Among the tested analogues,analogue **114** exhibited potent anti-TB activity against *M. tuberculosis*, having a MIC value of 2.5-5 µg/ml. Results revealed that such hybrid analogues provide an efficient approach for future pharmacological developments to fight against tuberculosis [21].



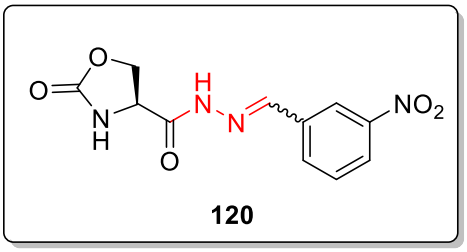
114

Pinheiro *et al* (2011), explored a series of *L*-serniylhydrazone derivatives and screened for their*in-vitro* antitubercular activity towards *Mycobacterium tuberculosis* H37Rv. Generally,the tested analogues were tested for antitubercular activity and showed good activity. The compounds **115-120** showed remarkable activity in the range of MIC 25 and 100 µg/ml, and were comparable with standard antitubercular drug D-cicloserine (5-20 µg/ml) [108].



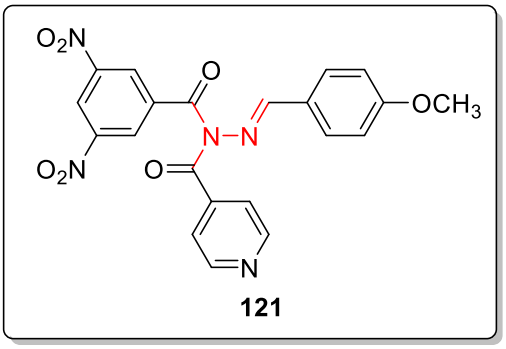
115-119

Comp	R_1	R_2	R_3
115	H	NO_2	H
116	H	CN	H
117	OH	OH	H
118	OH	H	OH
119	OH	OCH_3	H



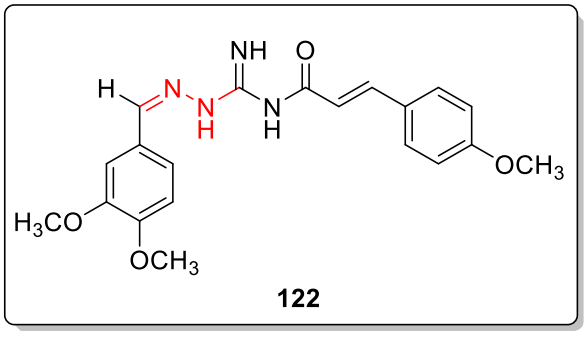
120

Kumar *et al* (2010), identified a novel series of benzoic acid hydrazonesand their nicotinyl derivatives. The synthesized analogues were assayed*in-vitro* for their anti-tubercular activities against *Mycobacterium tuberculosis* strain. It was revealed that compound **121**showed the most potent anti-tubercular activity with MIC value of 3.5×10^{-3} µM [109].



121

Bairwa *et al* (2010), reported the synthesis of a novel sequence ofphenylacrylamide analogues substituting cinnamic acid and guanylhydrazonesby employing microwave-assisted synthesis. Resazurin-microtitre plate assay (REMA) was used to evaluate the anti-tubercular activity of compounds against *Mycobacterium tuberculosis*. Results demonstrated that compound **122** is of particular interest having good safety profile with MIC of 6.48 µM. In future,the compound can be used for assisting antitubercular studies[110].



122

5. RECENT PATENTS FILED/GRANTED ON HYDRAZONE DERIVATIVES

S. No.	Date of Publications	Patent Number	Inventions Disclosed	References
1.	07/11/2017	US 9,809,550 B2	Quinolyl hydrazones for the treatment of tuberculosis and related diseases.	[111]
2.	14/03/2017	US 9,593,103 B2	Pyridyl hydrazones for the treatment of tuberculosis and related diseases.	[112]
3.	15/09/2015	US 9,133,230 B2	Hydrazone derivatives having potent antitumor activity toward multi-drug resistant tumor cells.	[113]
4.	07/01/2014	US 8,623,849 B2	Medicinal applications of benzoic acid hydrazonessynthesizedon the basis of steroidal tigogenin.	[114]
5.	30/07/2013	US 8,497,296 B2	N, N'-hydrazino-bis-isatinderivatives withselectiveactivity against multidrug-resistant cancer cells.	[115]
6.	24/01/2012	US 8,101,649 B2	N-acyl hydrazonederivatives useful as modulators of nicotinic acetylcholine receptors.	[116]
7.	06/04/2010	US 7,692,030 B2	Conjugates of artemisinin-related endoperoxides and hydrazonederivatives for the treatment of cancer.	[117]
8.	20/08/2009	US2009/0208374 A1	Novel silane compounds carrying a hydrazone or diazo functional group in order to functionalize solid supports and immobilize biological molecules on these supports.	[118]
9.	01/04/2008	US 7,351,831 B2	Process for asymmetric intramolecular (3+2) cyclo-addition of hydrazones.	[119]
10.	11/10/2007	US 2007/0238700	N-phenyl-1,1,1-trifluoromethane-sulfonamide hydrazone compounds and	[120]

		A1	their usage in controlling parasites.	
11.	07/12/2006	US 2006/0276433 A1	Hydrazone derivatives.	[121]
12.	09/12/2003	US 6,660,737 B2	Medicinal uses of hydrazones.	[122]
13.	18/03/2003	US 6,534,502 B2	Substituted oximes and hydrazonesas neurokinin antagonists.	[123]

6. CONCLUSION

The invention of novel chemotherapeutic agents is an essential and challenging task for the medicinal chemists and several research programs are directed towards the design and synthesis of newer drugs for their chemotherapeutic usage. To discover active analogues towards multidrug-resistant microbial infections, hydrazone containing analogues are found as an important class for the development of newer anti-infective drugs. Hydrazone ligands attracted the special attention of researchers due to their well-known chelating capability, structural flexibility and diverse range of pharmaceutical applications. The present review highlights the potential of hydrazone derivatives as a guideline for the advancement of anti-infective agents, SAR based study of hydrazone analogues with a diverse mechanism of action of nanoparticles based hydrazone compounds as potent anti-infective agents have been addressed in effective way.Various conventional and green synthesis of hydrazone derivatives and recents patents filed or granted on hydrazone compounds as anti-infective agents have also been tabulated. It could be observed that with careful designing of known hydrazone derivatives and future work might yield more promising lead compounds with better anti-infective activity.

7. FUTURE ASPECTS:

Hydrazone is indeed one of the primary drug research scaffolds due to its remarkable therapeutic properties. In heterocyclic chemistry, the expansion of effective and reliable methods for their synthesis and fusion with many other bioactive molecules has ensured that hydrazones have been a crucial moiety. Research thresholds will therefore remain crucial to the discovery of bioactive

molecules in order to satisfy all the relevant criteria for the expansion of potent antiviral and antimicrobial drugs. Current and re-emerging infectious diseases will continue to present significant challenges to global health into the 21st century. According to world health organization (WHO) study, these are already considered as leading cause of death and affected patient health care system across the world. Because of the rising number of infections and resistance towards conventional treatments, there is an persistent need to produce some useful medications that can counter resistance and side-effects related to anti-infective medications. In addition, rational design and production of the novel anti-infective agents that contain this scaffold will help to resolve increasing microbial resistance problems and satisfy the need for successful antimicrobial therapy to combat multiple deadly microbial infectious diseases. Based on the literature survey, we ascertained that the future of medicinal chemistry should focuses on the development of newer molecules with innovative approach in order to obtain therapeutically active molecules in forthcoming future. The development of such new molecules includes new synthetic instruments, synthetic strategies and techniques.

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CONFLICT OF INTEREST

There are no conflicts of interest in this article.

ABBREVIATIONS

HAV	Hepatitis-A Virus	IR	Infrared
ATCC	American Type Culture Collection	NMR	Nuclear magnetic resonance
DNA	Deoxyribonucleic Acid	SAR	Structure-activity relationship
MRSA	Methicillin-resistant Staphyloccous aureus	REMA	Resazurin Microtiter Assay Plate
MAOS	Microwave-assisted organic synthesis	MTCC	Microbial Type Culture Collection

TMV	Tobacco mosaic virus	MIC	Minimum inhibitory concentration
µM	Micromolar	MBC	Minimum bactericidal concentration
Mm	Millimeter	ETV	Entecavir
Nm	Nanometer	LORA	Low Oxygen Recovery Assay
µg/ml	Microgram per millilitre	FBHZ	Ferrocenylhydrazone
MABA	Microplate Alamar Blue Assay	ROS	Reactive oxygen species
HRMS	High Resolution Mass Spectrometry	TZM-*bl*	Hela cell line
HIV	Human Immunodeficiency Virus	EC_{50}	Half maximal effective concentration
SI	Standard international	INH	Isoniazid
ROD	Varicella-Zoster Virus strain		

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: